Answer 1:

Bibliographic Information

Potential therapeutic for chronic myelogenous leukemia by a polyamide-chlorambucil conjugate. Chou, C. James; Alvarez, David; Farkas, Michelle E.; Burnett, Ryan; Dervan, Peter B.; Gottesfeld, Joel M. Departement of Molecular Biology, The Scripps Research Institute, La Jolla, CA, USA. Abstracts of Papers, 232nd ACS National Meeting, San Francisco, CA, United States, Sept. 10-14, 2006 (2006), AEI-015. Publisher: American Chemical Society, Washington, D. C CODEN: 69IHRD Conference; Meeting Abstract; Computer Optical Disk written in English. AN 2006:855567 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Chronic myelogenous leukemia (CML) is caused by the genetic rearrangement of Bcr and Abl genes to give rise to a highly active fusion P210BCR-ABL tyrosine kinase. The development of selective p210BCR-ABL tyrosine kinase inhibitor Gleevec (STI 571, Imatinib mesylate, Norvartis) as a directed therapeutic for CML has been a major advace in cancer therapy. However, many Gleevec patients acquire mutations confirming drug resistance as well as Bcr-Abl-independent genetic abnormalities while on Gleevec treatment. We have developed a lead polyamide-chlorambucil conjugate, 1R-Chl, that down-regulates a specific gene encoding a key component of cellular chromatin, histone H4c, in both CML cell culture and in a mouse xenograft model. Histone H4c is over-expressed in a variety of cancers, including CML, and may represent a new target for cancer chemotherapy including leukemia. 1R-Chl is a sequence specific alkylator capable of discriminating a single base pair mismatch in DNA, and inhibits tumor cell growth in both CML cell cultures and in the mouse model without significant toxicity to the animals. Only slight down-regulation (.apprx.10 to 20%) of p210BCR-ABL mRNA level was obsd. suggesting the growth inhibition is independent of p210BCR-ABL kinase. Similar growth inhibition was obsd. using siRNA targeting histone H4c; however, the siRNA down-regulation only causes G1/S arrest while 1R-Chl induces G2/M arrest. Nevertheless, polyamide 1R-Chl is a strong candidate for cancer therapy and histone H4c plays a key role in leukemia growth inhibition.

Answer 2:

Bibliographic Information

Antitumor activity and pharmacokinetics of estra-1,3,5 (10)-triene-3,17 beta-diol, 3-benzoate, 17-((4-(4-bis(2-chloroethyl)amino)phenyl)-1-oxobutoxy) acetate) (Bestrabucil) in human tumor xenografts serially transplanted into nude mice. Kubota T; Kawamura E; Suzuki T; Yamada T; Toyoda H; Miyagawa T; Kurokawa T Japanese journal of clinical oncology (1986), 16(4), 357-64. Journal code: 0313225. ISSN:0368-2811. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 3795532 AN 87087277 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Bestrabucil (KM2210), the benzoate of an estradiol-chlorambucil conjugate, was used experimental cancer chemotherapy against 13 human tumor xenografts serially transplanted into nude mice, and its pharmacokinetics was studied. The tumors were one esophageal, two gastric, six colon, one cholecystic and three breast carcinomas. Two tumor tissue fragments approximately 3 X 3 X 3 mm were inoculated into BALB/cA nude mice, which were then treated with KM2210 at doses of 100, 200 and 300 mg/kg/day orally starting 24 hr after the transplantation or when the tumor reached a weight of 100-300 mg. The concentration of KM2210 and its derivatives in the tumor xenografts, normal muscular tissue and blood were assayed by high performance liquid chromatography. Six out of 13 xenografts were found to be sensitive to KM2210. The concentrations of KM2210 and its derivatives in the tumor tissues of the sensitive xenografts were five to 10 times higher than those in blood and muscular tissue, and the antitumor activity correlated well with the area under the curve of active metabolites of KM2210 in the tumor.